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(57) Abstract

Objects of the InventionThe lumen bypass pharmaceutical preparation excellent in the endurance to a mechanical and thermal destructive operation at a pelletizing process is provided.

Elements of the InventionLumen bypass pharmaceutical preparation for ruminants by which a biological activity substance being included in a molded product which has synthetic thermoplasticity polymer or a copolymer, and acid dissolved solids of nonaqueous solubility. EffectA feed pellet including lumen bypass pharmaceutical preparation can mass-produce now using a pellet mill.

Claim(s)

Claim 1 Lumen bypass pharmaceutical preparation for ruminants by which a biological activity substance being included in a molded product which has synthetic thermoplasticity polymer or a copolymer, and acid dissolved solids of nonaqueous solubility.

Claim 2The lumen bypass pharmaceutical preparation according to claim 1 being at least one sort chosen from a group which synthetic thermoplasticity polymer or a copolymer of nonaqueous solubility becomes from polyethylene, polypropylene, an ethylene-vinyl acetate copolymer, and polyester.

Claim 3The lumen hypass pharmaceutical preparation according to claim 1 or 2, wherein acid dissolved solids are 1.5 in lumen bypass pharmaceutical preparation 100 weight section weight section -60 weight sections.

Claim 4The lumen bypass pharmaceutical preparation according to claim 1 or 2, wherein acid dissolved solids are mineral.

Detailed Description of the Invention

Industrial ApplicationThis invention relates to the lumen bypass pharmaccutical preparation which has endurance to the influence of the mechanical stress in a pelletizing process, or heat and which can be pelletized in more detail with respect to the lumen bypass pharmaccutical preparation for ruminants.

0025/ince the lumen bypass pharmaceutical preparation of this invention can carry out the lumen bypass of the biological activity ingredient, and can be made to be able to reach in a moving object and it can moreover pelletize with other feed by a pellet mill (it has pelletizing-proof nature), it is nutritionally and clinically adapted for the various feed methods as useful feed, and can use for ruminants, such as a cow and a sheep.

0003

Description of the Prior ArtSpread is progressing when breeding a ruminant from beneft nutritional prescribing lumen bypass pharmaceutical preparation for the patient with feed, and clinical. However, complicatedness etc. of work which carries out the measuring salary of the problem and lumen bypass pharmaceutical preparation of palatability of lumen bypass pharmaceutical preparation to ruminant each were made into the problem. As what, on the other hand, enables mitigation and automation of feed work a feed pellet, spread is progressing increasingly in recent years.

0004Therefore, if the feed pellet which includes lumen bypass pharmaceutical preparation as the constituent is put in practical use, it will be expected that it becomes the useful feed which harmessed both advantage.

0005The lumen bypass pharmaceutical preparation for ruminants Various amino acid, various vitamins, While it is the pharmaceutical preparation having contained kinds of other biological activity substances, or these two sorts or more and elution of the biological activity substance in the lumen (rumina) of a ruminant or decomposition by a microorganism is restricted, it has a function which enables elution and absorption of the biological activity substance in the digestive organs after the abomasum. There are already many the concepts and examples of lumen bypass pharmaceutical preparation, and they are publicly known. of a thing

0006-lowever, it is thought that these lumen bypass pharmaceutical preparation is constituted without having almost no intention of pelletizing which uses a pellet mill.
0007Although this invention persons showed the part according to the below-mentioned comparative example, they made these publicly known lumen bypass pharmaceutical preparation as an experiment, and produced the feed pellet from trial production lumen bypass pharmaceutical preparation and feed by the pellet mill. However, the thing of the form which carried out protective coating of the particles of a bloogical activity substance,

It was destroyed, so that a prototype was not stopped between the pelletizing processes to which the thing of the form which distributed the biological activity substance also includes humidification and heat-treatment, and a mechanical work in oil and fat, and the lumen bypass nature was reduced to disappearance or an extreme, and practical capable nature was lost.

0008USP.5068108 Aithough it is what mixed a polymeric material and fats and oils and formed lumen bypass pharmaceutical preparation and an item has the statement of the concept of pelletizing-proof, The performance of the lumen bypass pharmaceutical preparation itself, the evaluation result of the lumen bypass nature after pelletizing, etc. do not have that the pharmaceutical preparation presentation is only indicated and a statement in an example in any way.

0009Although this invention persons referred to the example of USP5068108 and examined it, the pharmaceutical preparation of mechanical intensity which mixed a polymeric material and fats and oils was insufficient, and it was destroyed, so that a prototype was not stopped at the pelletizing process in the pellet mill, and lumen bypass nature disappeared.

0010The method of giving the function of pelletizing-proof nature for thermoplastic polymer or the thermoplastic copolymer (it is hereafter described as this thermoplastic polymer), and acid dissolved solids of nonaqueous solubility as a constituent of lumen bypass pharmaceutical preparation is not publicly known. Why this thermoplastic polymer was not used as a constituent of lumen bypass pharmaceutical preparation, if there is no factor of pelletizing-proof, lumen bypass nature, and the elution after the abomasum and absorptivity can be balanced more easily than these, and it will be considered since there were many other constituents useful also as feed.

0011

Problem(s) to be Solved by the InventionThis invention was made in view of the problem of the above conventional technologies, the place made into the purpose puts in practical use the feed pellet which includes lumen bypass pharmaceutical preparation, the advantage of both the above lumen bypass pharmaceutical preparation and a feed pellet is utilized, and it is in canceling a problem. It becomes possible to utilize the benefit as feed for ruminants, such as a cow and a sheep, as the result.

0012

Means for Solving the ProblemThis invention persons made polyethylene, polypropylene, and this thermoplastic polymer like an ethylene-vinyl acetate copolymer contain a biological activity substance for a trial, and made pharmaceutical preparation as an experiment for it. Elastic moduli in dynamic viscoelasticity measurement (30 **, 30 Hz) of this trial production pharmaceutical preparation are 10 ° - 10 °Pa, there is no brittleness in pharmaceutical preparation, and character of elongation peculiar to this thermoplastic polymer was also held.

0013When this trial production pharmaceutical preparation is pelletized using a pellet mill with feed, at a pelletizing process that shape, Although it changed, it was not ground, and the elution nature of a biological activity substance in inside of a lumen of the feed pellet was maintaining a level of pharmaceutical preparation before pelletizing, while it had been very low, and these trial production pharmaceutical preparation found out having the outstanding pelletizing-proof nature. However, these synthetic resins had elution after abomeasum, and poor absorptivity.

00.14Then, if acid solubility is given to this thermoplastic polymer, it dissolves selectively by abomasum and a biological activity substance can be emitted, As a result of advancing examination further from an idea that lumen bypass nature is obtained, this invention persons are the methods of adding a substance of acid solubility for a biological activity ingredient to this thermoplastic polymer, it found out that pharmaceutical preparation having elution after the target pelletizing-proof nature, lumen bypass nature, and absorpsivity was obtained, and this invention was reached.

0015 Lumen bypass pharmaceutical preparation in this invention does not have restriction in particular in its structure and composition. Although there is no restriction in particular also about shape, the shape of a ball and cylindrical shape can be considered. Although

restriction in particular does not have a size, either, particle diameter It is thought that 0.5-3.0 mm is suitable.

0016Composition ratio of a biological activity substance in lumen bypass pharmaceutical preparation in this invention is ten to 50 weight section preferably one to 70 weight section among lumen bypass pharmaceutical preparation 100 weight section. The validity of a biological activity substance is scarcer in a small quantity than in this range, and it becomes impossible to prevent elution in a lumen in many ranges.

0.01.7Although 99 to 30 weight sections (preferably 90 to 50 weight section) of the remainder are this thermoplastic polymer and acid dissolved solids, they can be selectively transposed to an additive agent for refining. 90 to 50 weight section and acid dissolved solids of composition ratio of this thermoplastic polymer in the remainder are ten to 50 weight sections preferably five to 60 weight section 95 to 40 weight section. Quantity of a refining additive agent which can be replaced selectively is 30 or less weight sections of the remainder. Out of these ranges, balance of lumen bypass nature, and elution after abomasum and absorptivity becomes poor.

00.18As a biological activity substance used for this Invention, Sugars, such as a salt of amino acid, such as methionine and lysine, and amino acid, a dimer and a polymer of amino acid, an amino acid derivative and a salt of MHA(methionine hydroxy analog) MHA, various vitamins, grape sugar, and sucrose, hormone, an enzyme, an animal drug, an antibiotic, a vaccine, etc. are mentioned.

00.19This thermoplastic polymer used for this invention is with an average molecular weights of 10,000 or more which can be fabricated by heat melting polymer, a copolymer, and condensation polymer/sation polymer, and does not dissolve in water substantially. As the example, polymer of olefins, such as polyethylene, polypropylene, and polyisobutylene, Condensation polymer/sation polymer, such as polymer, such as a copolymer of olefins, such as ethylene-vinyl acetate, 1,2-polybutadiene, polyvinyl acetate, and poly(meta) acrylic ester, a copolymer, polyamide, and polyester, etc., are mentioned.

0020In pH five to 8 neutral region, acid dissolved solids in this invention do not dissolve in water substantially, but refer to a substance which dissolves in water in pH three or less acidic regions.

002.1As an example of acld dissolved solids used for this invention, Polymers of natural product origin of a kitchen, chitosan, calcium alginate, etc., Polymiyl-acetal diethylamino acetate, a dimethylaminoethyl methacrylate methylmethacrylic acid copolymer, Mineral, such as synthetic macromolecules, such as vinylpyridine styrene copolymer, calcium carbonate, magnesium carbonate, calcium secondary phosphate, calcium pinosphate, calcium pinosphate, acidium pinosphate, acidium pinosphate, acidium pinosphate, acidium pinosphate, acidium pinosphate, acidium pinosphate, and lead carbonate, etc. are mentioned.

0022In this invention, a refining additive agent other than the above, etc. can be added. As an example of this refining additive agent that can be replaced selectively, powder of polymer and oligomer various additive agents, such as stabilizer, perfume, sweetners, a coloring agent, and a palatability improving agent, and for refining, a plasticizer, a grinding thing and a staple fiber thing of various feed, and an inorganic substance, etc. are mentioned.

0023Aithough a manufacturing method of lumen bypass pharmaceutical preparation of this invention does not have limitation in particular and various molding methods used for plastic molding can be used, biaxial extruder to which a rotary blade was attached is mentioned to a delivery as an example.

0024A pellet in this invention is a thing of a roller extrusion type called a pellet mill widely used in the feed industry, After feed etc. which are pelletized are thrown in by Popper and are subsequently humidified and heated by steam, while passing through inside of a hole, being continuously pushed into a hole of a pellet die and being mechanically pushed on it with a roller, it is a thing of form which becomes a hard feed pellet (hard pellet). A name was decided by a size and a manufacturing process of various granulation articles, and a pellet as used in the feed industry means a feed granulation article manufactured in the form of the above.

0025

Example: An example and a comparative example explain this invention still in detail. However, the range of this invention does not receive any restriction according to the following examples.

0026A) Methionine 30 weight section which has the shape of production (A-1) powder of lumen bypass pharmaceutical preparation, Low-density-polyethylene (M14 Nippon Oil chemicals) 40 granular weight section, chitosan (LLWP Kimitsu chemicals) 5 weight section, and calcium carbonate 25 powdered weight section were mixed, and it put into the hopper of the extruder which attached the rotary blade to the delivery. The barrel temperature of extruder was 210 **, delivery temperature was 190 **, and almost spherical pharmaceutical preparation with a particle diameter of about 1.5 mm was obtained. 0027(A-2) Methionine 28 granular weight section, the amount part of vitamin-E acetate duplexs, Ethylene-vinyl acetate copolymer (EVAFLEX EV360 Mitsul E. I. du Pont de Nemours Porl Kem Cal) 50 granular weight section and calcium phosphate 20 powdered weight section were mixed, and it put into the hopper of the extruder winto attached the rotary blade to the delivery. The barrel temperature of extruder was 140 **, adelivery temperature was 130 **, and almost spherical pharmaceutical preparation with a particle diameter of about 1.2 mm was obtained.

0.28(A-3) Polypropylene (709HK Ube Industries) 50 granular weight section, chitosan (LLWP Kimitsu chemicals) 10 weight section, and calcium carbonate 10 weight section were mixed, and, subsequently addition mixing of MHA15 powdered weight section and the lysine 15 weight section was carried out. This was put into the hopper of the extruder which attached the rotary blade to the delivery, the barrel temperature of extruder was 210 **, delivery temperature was 190 **, and almost spherical pharmaceutical preparation with a particle diameter of about 2 mm was obtained.

00.29(A-4) Calcium salt 30 weight section of MHA, and granular polyester (Byran 200 Toyobo) 40 weight sections, Dimethylaminoethyl methacrylate methylmethacrylic acid copolymer 20 weight section, It put into the hopper of the extruder which mixed calcium-secondary-phosphate 10 weight section and with which the rotary blade attached this to the delivery, and the barrel temperature of extruder was 210 **, delivery temperature was 190 ***, and almost spherical pharmaceutical preparation with a particle diameter of about 2 mm was obtained.

0030(C-1) The heating and dissolving of 54 degrees of beef tallow hydrogenated oil (Nippon Oil & Fats) 25 weight section and the beef tallow extreme hydrogenated oil (Nippon Oil & Fats) 26 weight section are carried out. Stirring in a mixer, methionine 28 weight section, the amount part of vitamin-E acetate duplexs, chitosan 4 weight section, calcium carbonate 8 weight section, and calcium-primary-phosphate 7 weight section are added, mixed suspension was carried out, and the melting slurry was made. Feeding cold blast from the lower part of a 20-m-high void tower, from the crowning, it sprayed and this slurry was corned. The screen exception carried out the obtained granulation thing, and lumen bypass pharmaceutical preparation with a particle diameter of 0.6-1.4 mm was obtained. 0031(C-2) Mean particle diameter is 0.5-0.7-mm 98%. Methionine particles of concentration 350 q 88 q of stearic acid (melting point 68-69 **), 2-vinylpyridine / styrene (70:30) copolymerization polymer 22 q, 1,2-dichloroethane 500 q, ethanol 500 q, spray for preventing static electricity It coated with the solution which consists of 3 ml with the fluidized bed process, and lumen bypass pharmaceutical preparation was produced. 0032- The pelletizing examination following condition pelletized and estimated the abovementioned lumen bypass pharmaceutical preparation. Feed: In an exam, since there being almost no obstacle in the case of measurement of an elution rate, and extraction and observation of pharmaceutical preparation in a pellet are easy, use raw rice rice bran. pellet-mill: -- aperture of a 50 H.P. die: -- composition ratio of 4 mm lumen bypass pharmaceutical preparation: -- 2.5% die temperature: -- 75-85 ** 0033- The pharmaceutical preparation before and behind pelletizing was evaluated about the evaluation test following item.

Mc elution rate: It is a ratio to the amount of active substances among the pharmaceutical

preparation of the amount of active substances eluted in Mc liquid when pharmaceutical preparation or a feed pellet was immersed in Mc liquid and shaken for 24 hours, and equivalent to the elution volume in a lumen.

CL elution rate: — Mc — equivalent when a ** exception carries out a solid after elution rate measurement, the solid is immersed in CL liquid and it shakes for 3 hours, it is a ratio to the amount of active substances among the pharmaceutical preparation of the amount of active substances eluted in CL liquid, and to an abomasum elution volume.

Mc liquid: Solution which was the liquid corresponding to rumina gastric juice, dissolved 0.12 g of 9.30 g of sodium bicarbonate 9.8g, 0.57 g of potassium chloride, and disodium phosphate 12 monohydrate, 0.47 g of sodium chloride, and magnesium sulfate 7 monohydrates in water, and set the whole quantity to 1.1.

CL liquid: Solution which is the liquid corresponding to abomasum gastric juice, and added water to 50 ml of 0.2N potassium chloride, and 10 ml of 0.2N chloride to make 200 ml. 0034- Extrusion molding of the pharmaceutical preparation presentation of the rate measurement examples 1-4 of dynamic viscoelasticity was carried out to round bar shape about 5 mm in dlameter, and it cut in length of about 5 cm, and was considered as the sample. It is LEO Vibron about a sample. The elastic modulus was measured in 30 Hz and 30-150 ** using DDV-III-EA (cage ene tech company). The elastic modulus (Pa) at 30 ** was shown in Table 1. In the presentation of the comparative example, the molded product was weak and was not able to produce a sample suitable for measurement.

Table 1

0036

Effect of the InventionAs shown in Table 1, in the lumen bypass pharmaceutical preparation of C-1 and C-2, as for each thing pelletized by the pellet mill, lumen bypass pharmaceutical preparation is destroyed, the lumen bypass nature falls extremely, and it is already impractical. On the other hand, the pelletizing-proof pharmaceutical preparation of A-1 to A-4 by this Invention is maintaining lumen bypass nature with modification of shape good also after the pelletizing process of a certain thing, and the solubility after the abomasum.

It was admitted that there was pelletizing-proof nature.

0037By this invention, it became conventionally utilizable a feed pellet including the lumen bypass pharmaceutical preparation which was not able to be put in practical use. This invention obtains lumen bypass pharmaceutical preparation using the pelletizing-proof nature of synthetic thermoplasticity polymer of nonaqueous solubility, or a copolymer, and the feed pellet which, as a result, includes lumen bypass pharmaceutical preparation can mass-produce it now easily by the conventional pellet mill.